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#### Introduction

# Highly enantioselective access to diketopiperazines via cinchona alkaloid catalyzed Michael additions<sup>†</sup>

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Michael addition reactions of triketopiperazine (TKP) derivatives to enones, mediated by a cinchona alkaloid-derived catalyst, deliver products in high yield and enantiomeric ratio (er). Use of unsaturated ester, nitrile or sulfone partners gives bridged hydroxy-diketopiperazine (DKP) products resulting from a novel Michael addition-ring closure.

Diketopiperazines (DKPs) have acquired the status of privileged structures for medicinal chemistry, for example tadalafil (or cialis®, 1) is a potent PDE5 inhibitor used for treating male erectile dysfunction, Fig. 1.1

The DKP structure is also prevalent in many types of peptide antibiotics, including the clinically significant compound bicyclomycin (2), which has an interesting [4.2.2] ether-bridged core.2

Many other important natural product families incorporate DKP motifs, for example the bicyclo[2.2.2]diazaoctane core structure features in the fungal metabolite stephacidin A(3), which displays potent and selective antitumour activity.3 The extensive studies of the synthesis and medicinal chemistry of DKPs and their occurrence in bioactive natural products have been described in a comprehensive review by Borthwick.<sup>4</sup>

Despite this background, access to enantiomerically pure DKPs has relied very heavily on chiral pool materials and, with the exception of studies aimed at stephacidins and related



Fig. 1 Structures of significant bioactive DKPs.

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natural products, reports of stereocontrolled access to a,adisubstituted systems are scarce.5

Herein, we describe highly enantioselective access to  $\alpha, \alpha$ disubstituted DKPs, including bridged products related to 2 and 3, by means of asymmetric Michael additions mediated by cinchona alkaloid catalysts.6 To date this field of organocatalysis has largely been limited to doubly activated Michael donors, such as malonates, β-diketones, and similarly acidic substrates,7 and the use of amidic donors has been scarcely explored.8 Key to our new chemistry is the finding that the under-explored triketopiperazine (TKP) motif provides exceptional activation for deprotonation, whilst also enabling facile access to DKP products through nucleophilic addition.9

#### Results and discussion

Both the doubly activated *a*-carboxymethyl TKP 4a, and the parent system 4b, were readily prepared using an established approach.96,10 Mindful of the challenge of engaging masked glycine 4b in this type of chemistry, initial screening focused on the doubly activated TKP 4a, using a limited range of alkaloid catalysts 5a-e, and with MVK as Michael acceptor, Table 1.

All of the catalysts explored gave good levels of conversion to the desired Michael adduct 6a within only 20 minutes at room temperature, with isolated yields being very high. Natural alkaloids quinidine (5a) and quinine (5b) gave interesting levels of enantioselection, with the modified thiourea system (5c)being slightly less selective.<sup>11</sup> The catalyst systems 5d and 5e, developed by the Deng group, having a free quinoline phenol and an alkylated C-9 secondary alcohol, immediately displayed exciting levels of selectivity, especially in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C.<sup>12</sup> As anticipated, pseudoenantiomeric catalysts 5d and 5e gave opposite enantiomers of the product 6a, in this case with very high selectivity. The use of only 1 mol% of catalyst 5d was still adequate to effect smooth conversion to product 6a without erosion of enantioselectivity (entry 9).13

When these partly optimised conditions were explored with alternative Michael acceptors, and then with the parent TKP 4b, we found some slight further tailoring of the conditions was

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<sup>*a*</sup> Minutes. <sup>*b*</sup> Isolated yield after chromatography. <sup>*c*</sup> Determined by HPLC analysis. <sup>*d*</sup> Reaction conducted using 1 mol% catalyst.

required. In particular, TKP **4b** showed a tendency towards double Michael addition, which could be controlled simply by reducing the reaction temperature to -20 °C. The use of this lower temperature in turn extended reaction times, particularly with  $\beta$ -substituted Michael acceptors, and required us to maintain catalyst loading at 10 mol%. Table 2 shows the results obtained with TKPs **4a** and **4b** with a range of acceptors, including MVK, acrolein and various enones.

Addition reactions with TKP **4a** gave excellent levels of asymmetric induction, with  $\text{er} \ge 97: 3$  (entries 1–7). The high selectivity observed for both aromatic and aliphatic enones, and for acrolein, is particularly notable. High yields were also obtained in reactions of TKP **4b**, although levels of enantiose-lection proved more mixed. The lower figures appear to be due to variable erosion of er in the configurationally unstable TKP products rather than inherently lower levels of asymmetric induction. Thus, re-exposure of isolated TKP **6i** to the catalyst **5d**, under the usual conditions, led to erosion of er from 96: 4 to 89: 11. This problem should be overcome by more closely monitoring individual reactions, or perhaps by use of more hindered catalysts.

Table 2 Michael additions of TKPs 4 using catalyst 5d



Entry	ТКР	R′	R	<b>6</b> <sup><i>a</i></sup> [%]	er <sup>b</sup>
1	4a	н	Ме	<b>6a</b> 99	99:1
2	4a	Н	Н	<b>6b</b> 99	$96:4^{c}$
3	4a	Н	Et	<b>6c</b> 90	97:3
4	4a	Н	cy-C <sub>6</sub> H <sub>11</sub>	<b>6d</b> 99	97:3
5	4a	Н	Ph	<b>6e</b> 98	99:1
6	4a	Н	<i>p</i> -C <sub>6</sub> H <sub>4</sub> Br	<b>6f</b> 98	99:1
7	4a	Н	<i>p</i> -C <sub>6</sub> H <sub>4</sub> OMe	<b>6g</b> 87	99:1
8	4b	Н	Ме	<b>6h</b> 80	93:7
9	4b	Н	Et	<b>6i</b> 86	96:4
10	4b	Н	cy-C <sub>6</sub> H <sub>11</sub>	<b>6j</b> 99	90:10
11	4b	Н	<i>p</i> -C <sub>6</sub> H <sub>4</sub> OMe	<b>6k</b> 93	88:12
12	4b	Ph	Ph	<b>6l</b> 98	$99:1^{d}$
13	4b	Ph	o-C <sub>6</sub> H <sub>4</sub> Br	<b>6m</b> 91	$88:12^{d}$



Notwithstanding these issues, the er values for MVK and EVK (entries 8 and 9) are good, and entry 12, involving chalcone as acceptor, demonstrates that excellent selectivities are still possible from the simple TKP **4b**. Notably, both chalcone products **6l** and **6m** were isolated as single diastereoisomers, and no minor isomers could be detected in the <sup>1</sup>H NMR spectra of the crude materials.

To our knowledge, these are the first enone Michael additions using a simple, non-benzylic, amidic donor,<sup>14</sup> and are unusual in giving masked  $\alpha$ -amino acid products retaining an  $\alpha$ hydrogen.

Following crystallisation, the absolute and relative configuration of adduct **6m**, generated from reaction of TKP **4b** and *ortho*-bromo chalcone, was determined by X-ray crystallography, Fig. 2.<sup>15</sup>

Interestingly, in the crystal there are two independent molecules of **6m** having different conformations around the newly formed C–C bond (only one is shown, see ESI<sup>†</sup> for the other one).

From the data available to date, we confidently expect that the absolute configuration of the other products **6** is analogous, *i.e.* (*S*) at the newly formed asymmetric centre at C-6 on the TKP ring.<sup>16</sup>

This outcome is in accord with the stereochemical model proposed by Deng, in which the catalyst serves to organize both of the Michael addition partners in an extended array.<sup>12</sup> This involves activation of the donor by enolate formation through the quinuclidine amine function, and a developing hydrogenbonded association between the Michael acceptor and the quinoline phenol, Fig. 3.



Fig. 2 The structure of one of the two crystallographically independent molecules of 6m, with ellipsoids drawn at the 50% probability level



Model for 5d-catalyzed Michael addition leading to 6m. Fig. 3

Application of the Deng model for chalcone systems requires a seemingly counter-intuitive placement of the  $\beta$ -phenyl substituent (R') endo with respect to the TKP ring (albeit a planar, all-sp<sup>2</sup> ring). That this arrangement is plausible is supported by the finding that one of the crystal structure conformations of 6m (Fig. 1) exhibits precisely the local conformation about the newly formed C-C bond, as shown in Fig. 2. This arrangement apparently tolerates substitution of the ahydrogen, Y = H, with an  $\alpha$ -CO<sub>2</sub>Me function, this possibly further organising the transition state by an additional hydrogen bond to the quinoline phenol.<sup>12e</sup>

The TKP ring in these chiral products is expected to be electrophilic at C-3, this carbonyl function being both part of an imide, and part of an α-dicarbonyl.9 Thus, we anticipate that varied manipulations of these compounds will be possible to give DKPs of various kinds, and by way of preliminary demonstration of this potential, we have transformed 6b into the ether bridged DKP 8, via diol 7, Scheme 1.

The use of NaBH<sub>4</sub> enabled reduction of the aldehyde in adduct 6b with concomitant regioselective TKP reduction, to give 7, which then underwent N-acyliminium cyclisation using TMSOTf to give 8.17 This sequence was used to convert 6b into an adduct more suitable for er determination, and the product 8 proved to be highly enantiomerically enriched (>96 : 4 er). This compound has a distinctive 4-atom ether-bridged DKP reminiscent of that present in the antibiotic bicyclomycin (2).<sup>2</sup>

We also established that reduction of TKPs to the corresponding DKPs could be achieved in very high overall yield by a two-step process involving initial reduction by L-selectride, then treatment with Et<sub>3</sub>SiH BF<sub>3</sub>-OEt<sub>2</sub>, Scheme 2.

The initial reduction proved highly regioselective for the C-3 TKP C=O function, even in the presence of a side-chain ketone. The hydroxy DKP 9 is an obvious precursor to an N-acyliminium type of intermediate, with many possibilities for further transformation.

In this case reduction under standard conditions gave DKP 10, the er of which (99:1) was found to be essentially the same as the starting TKP. This result is particularly significant for manipulation of these systems, since it demonstrates the possibility of converting a configurationally labile TKP into a less acidic, and so more configurationally stable, DKP product.

We subsequently extended our Michael addition studies to include other types of acceptor, including vinyl sulfone, acrylonitrile and acrylate esters. Reactions conducted using TKPs 4a and 4b with these partners provided bicyclic hydroxy DKP products 11 directly, via a novel Michael-ring-closure process,18 Table 3.

The greater nucleophilicity of the intermediate anions or enolates involved in these reactions, compared to those involving enones, is presumably the origin of the observed aldol-like ring-closure. Remarkably, this process delivers bridged DKP products 11 as single diastereomers, with the creation of three new stereogenic centres, and with extraordinary efficiency and very good selectivity, especially in the cases involving vinyl sulfone.19 In the case of the nitriles 11b and 11e it was found that the thiourea catalyst 5c also gives excellent results (entries 7 and 8).

These DKPs possess the bicyclo[2.2.2]diazaoctane core structure of stephacidin and related natural products, and the relative configuration at C-6 (stephacidin numbering - see 3) is also correct for the majority of this family of alkaloids. The potential of this new process to deliver intermediates capable of further elaboration towards bioactive relatives of naturally occurring alkaloids is clear.



Scheme 1 Conversion of Michael adduct 6b into bridged DKP 8.



Scheme 2 Regioselective reduction of TKP 6l to give DKP 10.

Table 3 Enantioselective Michael-ring-closure of TKPs 4



Entry	ТКР	Cat.	х	$11^{a}\left[\% ight]$	er <sup>b</sup>
1	4a	5d	$CO_2Me$	<b>11a</b> 98	87:13
2	4a	5 <b>d</b>	CN	11b 99	95:5
3	4a	5 <b>d</b>	$SO_2Ph$	11c 97	97:3
4	4b	5d	CO <sub>2</sub> Me	11d 89	83:17
5	4b	5 <b>d</b>	CN	11e 98	91:9
6	4b	5d	$SO_2Ph$	11f 82	93:7
7	4a	5c	CN	11b 88	7:93 <sup>c</sup>
8	4b	5 <b>c</b>	CN	11e 82	$1:99^{c}$

<sup>a</sup> Isolated yield of single diastereomer after chromatography. <sup>b</sup> Determined by HPLC analysis.<sup>c</sup> Enantiomeric structure to that shown.

### Conclusions

In conclusion, we have demonstrated the utility of the TKP motif in asymmetric cinchona alkaloid-catalyzed Michael additions to access various significant types of chiral DKP with high selectivities. We anticipate that this approach will enable the synthesis of many types of non-racemic TKPs, DKPs and derived structures, particularly those with fully substituted asymmetric centres, and further study of these systems is the subject of ongoing research in our laboratories.

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15 ESI.†

- 16 All of the products obtained using catalyst **5d** show negative specific optical rotations. We have also been able to determine the absolute configurations of **6l** and a dioxolane acetal derived from MVK adduct **6h** by X-ray crystallography (see ESI<sup>†</sup>).
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